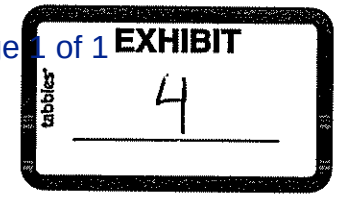

Laurenditerpenol, a new diterpene from the tropical marine alga **Laurencia intricata that potently inhibits HIF-1 mediated hypoxic signaling in breast tumor cells**

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The degree of tumor hypoxia correlates with advanced disease stages and treatment resistance. The transcription factor hypoxia-inducible factor-1 (HIF-1) promotes tumor cell adaptation and survival under hypoxic conditions. Therefore, specific HIF-1 inhibitors represent an important new class of potential tumor-selective therapeutic agents. A T47D human breast tumor cell-based reporter assay was used to examine extracts of plants and marine organisms for inhibitors of HIF-1 activation. Bioassay-guided fractionation of the lipid extract of the red **alga** Laurencia intricata yielded a structurally novel diterpene, laurenditerpenol (1). The structure of 1 was determined spectroscopically. The relative configurations of the substituents of each ring system were assigned on the basis of NOESY correlations. The absolute configuration of position C-1 was determined by the modified Mosher ester procedure (directly in NMR tubes). Compound 1 potently inhibited hypoxia-activated HIF-1 (IC50: 0.4 muM) and hypoxia-induced VEGF (a potent angiogenic factor) in T47D cells. Compound 1 selectively inhibits HIF-1 activation by hypoxia but not iron chelator-induced activation. Further, 1 suppresses tumor cell survival under hypoxic conditions without affecting normoxic cell growth. Compound 1 inhibits HIF-1 by blocking the induction of the oxygen-regulated HIF-1alpha protein. Mitochondrial respiration studies revealed that 1 suppresses oxygen consumption.